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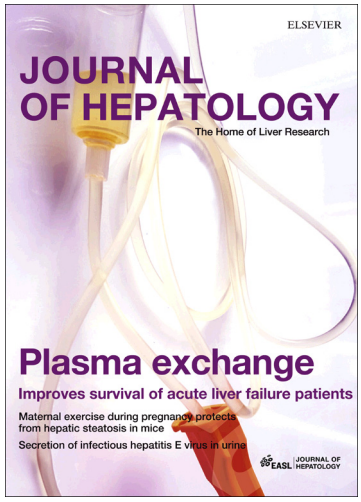

Review

ELITA consensus statements on use of DAAs in liver transplant candidates and recipients

Luca S Belli, Christophe Duvoux, Thomas Berg, Mario Strazzabosco, Stefano Fagiuoli, Saye Khoo, Georges Philippe Pageaux, Isabelle Colle, Massimo Puoti, Audrey Coilly, Didier Samuel, Marina Berenguer

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TITLE PAGE

ELITA consensus statements on use of DAAs in liver transplant candidates and recipients.

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LSB organized the ELITA monothematic Conferences, manuscript writing, critical review for intellectual content and approval of the manuscript.
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KEY WORDS
Direct Antiviral Agents, Liver Transplantation, Liver Transplant Candidate, Liver Transplant Recipient, Recurrent hepatitis C

LIST of abbreviations

Drug abbreviations. SOF: sofosbuvir. LDV: ledipasvir. DCV: daclatasvir. VEL: velpatasvir. GZR: grazoprevir. EBR: elbasvir. SIM: simeprevir. 3D: Paritaprevir/r, ombitasvir, dasabuvir. 2D: Paritaprevir/r, ombitasvir

Other abbreviations. HCV: hepatitis c virus. LT: liver transplantation. PEG-IFN: pegylated interferon. DAA: direct acting agents. DDI: drug to drug interactions. SVR: sustained virologic response. RAS: resistance associated substitution. AUC: area under the curve. M-TOR: mammalian target of rapamycin. LLOQ: lower level of quantification. HBV: hepatitis B virus. SmPC: summary of product characteristics. CsA: Cyclosporin. TAC: tacrolimus. MMF: micophenolate-mofetil. CNI: calcineurin inhibitors. IS: immunosuppressants. CNS: central nervous system. FCH: fibrosing cholestatic hepatitis.

The first version of these clinical practice guidelines was presented at the "ELITA Symposium" held in Brussels on September 13, 2015.

ABSTRACT

The advent of safe and highly effective direct acting antivirals (DAA) had huge implications for the HCV transplant field and changed our management of both, patients on the waiting list and those with HCV graft reinfection after Liver Transplantation (LT). When treating HCV infection before LT, HCV reinfection of the graft may be prevented in nearly all patients. In addition some candidates show a remarkable clinical improvement and are possibly delisted.

Alternatively, HCV infection can be treated post LT either soon after the transplant, taking advantage of the removal of the infected native liver, or at the time of disease recurrence as done in the past. In either case, some DAAs would have a limited use due to the frequent drug to drug interactions with various immunosuppressants and the many other drugs liver transplant recipients are often prescribed. In addition, some DAAs should be avoided in case of severe renal failure, which is not an unusual complication after LT.

The present document provides a series of "consensus statements" on the fore-mentioned LT issues that have not been extensively addressed previously. These statements have been developed in order to be of support to physicians and other stakeholders in charge of LT candidates and recipients when deciding to treat Hep C especially in difficult situations.

Background

Chronic hepatitis C virus (HCV) infection related advanced liver disease is the most common indication for liver transplantation (LT) which accounts for about 10% to 50% of LTs performed in northern and southern Europe, respectively (www.ELTR.org). Until very recently all HCV recipients who underwent LT had detectable viremia. Virtually all of them had HCV re-infection shortly after transplant. Between 10% to 30% developed cirrhosis within 5 years from LT and 40% presented signs of liver decompensation within 1 year from the diagnosis of recurrent cirrhosis (1-3). The combination of PEG-IFN and ribavirin has been the only therapeutic option available for the last 20 years but it was rarely effective, particularly in patients with more advanced graft hepatitis. Due to the high risk of severe disease recurrence, re-transplantation was controversial in case of HCV-induced graft failure. All these facts explain why HCV infected recipients had a reduced survival rate by at least 10% after 5 years of follow up, compared to non HCV infected individuals (4).

The advent of safe and highly effective direct acting antivirals (DAA) had huge implications for the HCV transplant field and changed our management of both, patients on the waiting list and those with HCV graft reinfection after LT. When treating HCV infection before LT, some candidates show a remarkable clinical improvement and are possibly delisted. If not, HCV reinfection of the graft may be prevented in nearly all patients when a HCV RNA negative status is achieved by DAAs at least 4 weeks before transplantation (>95%).

Alternatively, HCV infection can be treated post LT either soon after the transplant, taking advantage of the removal of the infected native liver, or at the time of disease recurrence as done in the past. In either case, some DAAs would have a limited use due to the frequent drug to drug interactions (DDI) with various immunosuppressants (IS) and the many other drugs liver transplant recipients are often prescribed. In addition, some DAAs should be avoided in case of severe renal failure, which is not an unusual complication after LT.

Finally, anti HCV positive donors with favorable histological features are likely to become an additional important resource for the donor pool particularly in areas the anti-HCV positive donors are more prevalent. The potential recipients of these grafts should be selected beforehand and treated after LT.

In the middle of this therapeutic revolution, two monothematic ELITA Conferences were held in Milan in March 2015 and April 2016 where a selected number of European experts discussed the many unsolved issues regarding the use of DAAs before and after liver transplantation. The present document provides the conclusions of these Conferences which are now included in these ELITA statements.

Methodology

The "Clinical practice guidelines" were elaborated following a slightly modified AGREE methodology (5). In brief, the promoter of this initiative was ELITA (European Liver and Intestine Transplant Association) which selected a scientific board of experts in charge of organizing the two Conferences held in Milan and of writing this document. The two Conferences were endorsed by the Italian Association for the study of the Liver (AISF) and by the European Association for the Study of the Liver (EASL). The scientific board defined the methodology utilized as well as the goals, and acted as developer and reviewer. The methodology chosen involved the following steps:

(a) The scientific board selected thirteen topics of interest and relevant questions regarding both

clinical practice and controversial areas.

(b) The scientific board also identified two working groups. The first addressed the issues related to "the management of the patient on the waiting list", the second "the treatment of post transplant HCV disease recurrence". The two working groups were composed of five experts guided by a group leader. The members of the two working groups were selected on the basis of competence, role, expertise and publications/research in the field of HCV and LT.

(c) The two group leaders together with the scientific board elaborated the provisional statements. All questions and provisional statements were circulated among the experts of each working group before the Conferences were held in Milan. This policy allowed each expert to independently carry out a systematic literature search, using Medline/ PubMed to support definitions and statements.

(d) The statements were discussed among the experts of the two working groups during 2 conferences held in Milan on 6th March 2015 and April 1rst, 2016 with the purpose to improve the quality of the statements. The two Conferences were videoed and all relevant comments were taken into account when preparing the final document.

(f) The scientific board prepared a draft of "Clinical Practice Guidelines" which incorporates the conclusions of the two Milan Conferences as well as the relevant data from existing publications and presentations at international meetings up to April 2016. For each of the 13 issues, a short background and a summary of the evidence is presented. The evidence and recommendations have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system (5). **Table 1**

(g) The first draft of the Clinical Practice Guidelines was eventually submitted to the experts of the working groups for corrections, comments and approval of the recommendations. Following a Delphi process the experts were asked to specify whether they approved each recommendation and, if not, to justify their disagreement. Corrections and comments were taken into account in the final version of the Clinical Practice Guidelines. Agreement among experts was very high (96%).

(h) The promoter, and all members of the scientific board and working groups were asked to declare any potential conflict of interests.

The questions selected by the scientific board are listed below:

Pre transplant phase.

1. Which DAAs should be used in cirrhotic patients listed for LT?
2. Which treatment schedules should be used in listed patients and what are the expected Sustained Virologcal Responses (SVR)?
3. What is the impact of pre LT DAAs on liver function and delisting?
4. Who should be treated or not treated before LT - patients with de-compensated cirrhosis.
5. Who should be treated or not treated before LT- patients with compensated cirrhosis and HCC
6. Is DAA therapy given across LT ("bridging therapy") a valuable option?
7. How to manage DAA treatment failures and when is detection of resistance associated substitutions (RAS) a concern?

Post transplant phase.

8. Which DAAs should be used after LT? The role of liver function, renal function and DDI.
9. What rate of SVR is expected after treating patients for HCV disease recurrence?
10. What is the best timing for DAA treatment after LT?
11. Can HCV therapy be expected to have a beneficial impact on extra-hepatic manifestations of HCV?
12. Is re-transplantation of HCV-infected recipients a reliable option under DAA therapy?
13. Can HCV-positive donors be used more extensively?

CLINICAL PRACTICE GUIDELINES.
A. Pre transplant phase.

Q1. Which DAAs should be used in cirrhotic patients listed for LT?

Background
DAAs should be used with caution in LT candidates with severely impaired liver function (Child-Pugh B and C) or with severe renal dysfunction (estimated GFR< 30 mL/min) as both conditions may affect the metabolism of some DAAs.

Facts
a. Impairment of liver function affects the exposure of various DAAs which is typically measured by the area under the curve (AUC) **(Table 2).**
Simeprevir (SIM): AUC increased by 2.5 fold in Child-Pugh B and 5.2 fold in and Child-Pugh C. *Paritaprevir/r* (ABT 450/r): AUC increased by almost 10 folds in Child-Pugh C. *Dasabuvir:* AUC increased by 4-fold in Child-Pugh C but not in Child B. *Sofosbuvir (SOF):* AUC increased by 2-fold both in Child-Pugh B and C. *Grazoprevir (GZR):* AUC increased by 2 to 3-fold in Child-Pugh B while there are no data to date for Child-Pugh C. *Ledipasvir (LDV)* and *Velpatasvir (VEL):* AUC not affected by reduced liver function.
b. Impairment of renal function impacts mainly the kinetics of the inactive metabolite of sofosbuvir, SOF007, which accumulates when the estimated GFR is below 60 mL/min. **(Table. 2).** In absence of sufficient safety data, the SOF summary of product characteristics (SmPC) warns against its use if eGFR is below 30mL/min.
c. Some DAAs share transport and metabolic pathways with several other drugs, including among others calcineurin, mTOR inhibitors and anti-retrovirals, which can cause strong DDI. The potential risk of DDI should be carefully taken into account before deciding on the most appropriate DAA regimen.
d. In patients with decompensated cirrhosis, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance. The dose of ribavirin should be adjusted downward by 200 mg at decrements if the haemoglobin level drops below 10 g/dl. Ribavirin administration should be stopped if the haemoglobin levels drops below 8.5 g/dl

Pre LT recommendations

1. SOF, LDV, VEL and Daclatasvir (DCV) can be used in patients with cirrhosis with no need of dose adjustment, regardless of liver impairment. GRADE I
Comment A note of caution is suggested when using DAA in patients with severe liver disease (Child-Pugh C or MELD > 20) due to limited experience

2. The 3D combo (Paritaprevir/r, ombitasvir, dasabuvir) and the 2D combo (Paritaprevir/r, ombitasvir) should not be used in patients with decompensated cirrhosis (Child-Pugh B and C). SIM is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and should be avoided in Child-Pugh C. GRADE I The 3D, 2D combo, SIM and GZR/EBR can be safely used only in patients with compensated cirrhosis (Child-Pugh A). GRADE II-2

3. In case of pre LT eGFR below 30 mL/min, SOF should be preferably planned after LT. GRADE III

4. DDI between a specific DAA and any other co-administered drug, should be carefully evaluated when planning any antiviral regimen.
Comment. Possible DDI should be checked on international websites (www.hepcdruginteractions.com) or discussed with a clinical pharmacologist GRADE III

Q2. Which treatment schedules are recommended for listed patients and what are the expected SVR?

Background
According to the Guidelines released by EASL and AASLD (6-8) different DAA regimens result in very high SVR rates even in patients with decompensated cirrhosis. Currently, many of these patients are treated while on the waiting list although it is not entirely clear how many of them will achieve viral eradication post LT. To date this issue has been addressed by a single study (9) which enrolled patients with compensated cirrhosis who were treated with a single DAA, SOF, in combination with Ribavirin.

Facts
Many studies have explored the efficacy of DAAs in terms of SVR in patients with various degrees of clinical decompensation (**Table 3**). Afdhal et al. (10) found that the combination of SOF/RBV for 48 weeks given to 50 Child-Pugh A or B, genotype 1 or 4, was associated with a 72% SVR overall (78% in Child-Pugh A and 68% in Child-Pugh B).
In SOLAR 1 study (11), the combination of SOF/LDV+RBV (600 mg, increased as tolerated) given to 108 patients with decompensated cirrhosis and infected with genotype 1 or 4, resulted in SVR-12 rates between 85 and 89%, irrespective of Child-Pugh class (B or C) and of treatment duration (12 or 24 weeks). In SOLAR 2 study (12) the same combination of SOF/LDV+RBV (600 mg, increased as tolerated) given to 160 cirrhotic patients for 12 or 24 weeks resulted in an SVR12 of 87-96% in Child-Pugh B patients and 72-80% in Child-Pugh C. The UK early access programme (13) on 467 Child-Pugh B or C patients, reported an overall SVR12 in 80% and 74% of patients treated with SOF/LDV +/- RBV or SOF/DCV+/- RBV (600 mg, increased as tolerated) for 12 weeks, respectively. Finally, the combination of SOF/VEL +RBV (1000-1200 mg) for 12 weeks in decompensated cirrhosis (mainly Child-Pugh B) resulted in an 85% SVR rate which was

superior to the 50% SVR rate achieved by combining SOF/VPV without RBV for 12 weeks or 24 weeks (14).

Looking at specific genotypes, the SVR12 was 80% in HCV genotype 1 or 4 with slightly higher SVR 12 rates when RBV was added. For HCV genotype 3 infected patients, the SVR12 was approximately 60% in those treated with SOF/LDV and 70% of those treated with SOF/DCV. (13)

The combination SOF+DCV+RBV (600 mg) for 12 weeks was also assessed in 113 pre and post LT patients with cirrhosis (any genotype) in the Ally1 study (15) which showed SVR12 rates of 92% in Child-Pugh A, 94% (30/32) in Child-Pugh B and 56% (9/16) in Child-Pugh C. Finally, another study of 55 genotype 1 patients treated with SOF+SIM showed SVR 4 rate of 75% (16).
In HIV co-infected patients, efficacy and tolerability of DAA treatments was similar to that observed in HCV monoinfected patients (17-18).
The effects of DAA given pre LT on post LT recurrence were explored in a single study by Curry et al. (9) who treated 61 HCC patients with Child-Pugh A cirrhosis with SOF/RBV. All patients were infected with genotypes 1 or 4 and were treated for either 48 weeks or until LT. The "on treatment" response was very high (93% had HCV-RNA less than the lower level of quantification (LLOQ) at week 4) and post LT SVR 12 was achieved in 70% of treated patients. In the same study a "post hoc" analysis showed a dramatic post-LT SVR 12 of 96% in the subgroup of 29 patients that had remained HCV-RNA negative for at least 30 days before LT. Indeed, of the 29 patients who had HCV-RNA below LLOQ for at least 30 days, only one (3%) suffered HCV recurrence after LT compared to 9 out 14 patients (64%) of those who had HCV-RNA below LLOQ for less than 30 days. These results suggest that the removal of the infected liver, once a viral clearance of at least 1 month duration has been achieved, is adequate for preventing HCV recurrence after LT and it indicates that achievement of SVR is not a mandatory end-point for all listed patients. To date this is the only study addressing virologic response profiles or kinetics required to prevent post LT HCV recurrence.

Pre LT recommendations

5. DAA therapy can be considered in patients who are listed for LT; virological response after DAA therapy is very high, in the order of 90%, in patients with compensated cirrhosis (Child-Pugh A) and high, in the order of 80%, in those with decompensated cirrhosis (Child-Pugh B-C) and is not influenced by HIV co-infection. GRADE I

6. The duration of DAA treatment should be as short as possible and DAA combinations achieving a SVR in 12 weeks should be preferred. GRADE III

7. A serum HCV RNA negative status (LLOQ) for at least 1 month before LT seems to be a reliable virologic end-point if prevention of HCV recurrence is the main treatment goal. Nevertheless, LT should not be postponed because of only short ongoing pre-LT DAA therapy, in case an organ becomes available. GRADE III
Comment. To date this virologic end-point has only been verified in patients with Child-Pugh A cirrhosis and therefore needs to be confirmed in patients with decompensated cirrhosis.

8. First line treatment options for listed patients according to specific genotypes are the following:
- *Genotype 1/4.* SOF/LDV+RBV (600 mg, increased as tolerated) or SOF+DCV+RBV for 12 weeks irrespective of liver function (Child Pugh A, B and C). SOF/VEL without RBV for 12 weeks in Child Pugh A and with RBV (1000-1200 mg) in Child-Pugh B and C. If patients do not tolerate RBV, the duration of SOF/VEL should be extended up to LT or to a maximum of 24 weeks. Other possible options for Child-Pugh A patients with genotype 1 are: SOF+SIM+RBV (600 mg, increased as tolerated) or 2D + RBV (600 mg, increased as tolerated) for 12 weeks or GZR/EBR for 12 weeks in HCV G1b, or GZR/EBR plus ribavirin for 16 weeks in HCV G1a patients. Finally in patients Child-Pugh A genotype 4 , 3D with (600 mg increased as tolerated) or without RBV for 24 weeks are equally valuable options. GRADE I
- *Genotype 2.* SOF+DCV for 12 weeks or SOF/VEL for 12 weeks are the preferred regimen for any listed patient infected with genotype 2 due to its short duration. In patients with Child-Pugh B or C RBV should be added. GRADE I
- *Genotype 3.* SOF/VEL + RBV (1000-1200 mg) for 12 weeks (Child-Pugh A, B) or SOF+DCV+RBV 1000-1200 mg for 12 weeks irrespective of liver function (Child-Pugh A, B and C). If patients do not tolerate RBV the duration of treatment of SOF/VEL or SOF+DCV can be extended up to LT or to a maximum of 24 weeks. GRADE II-2.
- Genotype 5-6. The same regimens with SOF/VEL, SOF/LDV or SOF+DCV suggested for genotype 1 or 4 should be used for genotypes 5 and 6 although data are limited. GRADE II-1

9. In HIV co-infected patients, the treatment options are identical to HCV mono-infected patients provided that DDI with concurrent antiretroviral therapy are taken into account . GRADE II-2

Q3. What is the impact of DAAs on liver function and de-listing?

Background

Up to one third of HBV patients with decompensated cirrhosis treated with Nucleos(t)ides drugs while listed for LT, can be eventually delisted within 1 year due to clinical improvement and, once delisted, they maintain their clinical improvement for up to 5 years (19). A critical issue is therefore to determine whether DAA treatment can also achieve similar results in HCV candidates with decompensated cirrhosis. The advantage of delisting HCV candidates would be twofold: for the patient who is delisted as he no longer needs a liver transplant and for the donor pool as an organ becomes available for another recipient.

Facts

Changes in liver function after DAA therapy given to patients with decompensated cirrhosis have been investigated in a limited number of studies (11-16), only 2 of which did not pool the pre and post transplant data together (12,16).

In the SOLAR 1 study (11) the combination of SOF/LDV+RBV was given for 12 or 24 weeks to 108 patients with decompensated cirrhosis and with genotype 1 or 4 infection. A decrease in Child-Pugh score of at least 2 points from baseline to post-treatment week 4 was observed in about 40% of the patients. This result was not influenced by the length of the treatment. These findings were also confirmed by the SOLAR 2 study (12).

In the ALLY 1 study (15), 48 decompensated cirrhotics (32 Child-Pugh B and 16 Child-Pugh C) were treated with SOF+DCV+RBV for 12 weeks. All 48 patients but 1 had a MELD < 25. Six of the 30 Child-Pugh B patients (20%), showed a decrease greater than 3 points in MELD at SVR 12. Among the 14 Child-Pugh C patients, a similar rate of improvement was observed in 3 cases (3/14, 21%). The study did not consider possible predictors of improvement nor the possibility of delisting. Virtually no patients with MELD score > 25 was considered eligible for DAA treatment in either study.

A study from France (20) explored the issue of delisting due to clinical improvement in 77 decompensated cirrhotics from 18 Centres. Patients were treated with various combinations of DAAs (SOF+DCV or LDV or SMV with or without RBV) for 12 or 24 weeks. Twelve patients (16%) were delisted due to clinical improvement. A similar delisting rate (18%) was reported in another study from Spain where 20 patients of the 110 treated with various combination of DAAs were delisted (21). A third European study promoted by ELITA (22) found that 21 of 103 (20.4%) patients with decompensated cirrhosis could be delisted due to clinical improvement after a median period of 60 weeks. The probability of being delisted was very high in patients with a MELD <16 (about 35%) and minimal in those with a MELD >20 (about 5%). All delisted patients had either a complete regression or a dramatic improvement of signs of hepatic de-compensation such as ascites and/or hepatic encephalopathy . Improvement of the MELD score by at least 3 points and of albumin by at least 0.5 gr/dL after 12 weeks of DAA, emerged as useful additional independent dynamic predictors of inactivation on the waiting list **(Fig 1)** and subsequent delisting. Despite these favourable results a word of caution is required for the following two reasons: 1. in candidates with high MELD score, a MELD decrease not sufficient for delisting may work at disadvantage for the patient that looses priority on the waiting list (MELD purgatory). 2. no data are yet available on how long the clinical improvement will last and on how many patients will develop a HCC after delisting. On the other hand, a drop of 2 to 3 points of MELD may be beneficial for the LT candidate by reducing the risk of mortality on the waiting list particularly in those with a medium/high MELD score and/or an expected prolonged waiting time.

Pre LT recommendations

10. Patients with decompensated cirrhosis and a MELD score < 20 on the waiting list should be considered for DAA therapy because around 20% of them can improve their liver function to an extent that they can be delisted. GRADE II-3
Comment: The benefit of delisting would be 2-fold, since a liver not used for a patient that is delisted can be offered to another LT candidate.

11. A minimal treatment period of 3 months should be considered before inactivation and delisting since the probability of being delisted due to clinical improvement depends not only on the MELD score before starting DAA therapy but also on MELD score and albumin improvements after 12 weeks of therapy *(details are given in recommendations 14 to 18).* GRADE II-3

12 In patients with high MELD scores (>20) and expected prolonged waiting time, the risk of a MELD purgatory effect should be balanced against the benefit of reducing the risk of death on the waiting list intrinsically associated with MELD reduction.
Comment A word of caution is required concerning possible side effects in patients with very advanced disease (MELD > 20) since DAA experience in treating these patients is very limited

Q4. Patients listed for decompensated cirrhosis (without HCC): who should be treated or not treated before LT?

Background
To establish whether pre LT DAA therapy is justified, the following factors should be considered:
- the risk of death on the waiting list, which is proportional to the MELD score.
- the possibility of clinical improvement after DAA, which may favour the delisting of some patients , typically those with low MELD scores.
- the awareness that a mild improvement in MELD score after DAA may not be enough for delisting and may work as a disadvantage for patients that lose priority on the waiting list. This MELD purgatory effect is typically observed in patients with high MELD scores.
- cost-effectiveness considerations.
- potential side effects as some case series show liver failure during DAA +/- RBV
- local epidemiology and HCV-positive donor policies **Fig.2**
Being aware of these factors will limit futile DAA treatment.

Facts
A significant decrease in either Child-Pugh or MELD score has been reported in 20% to 40% of patients with decompensated cirrhosis treated with DAAs. However this improvement may not be sufficient for delisting, particularly in Child-Pugh C patients with high MELD scores where the MELD purgatory effect is likely to be the highest. Factors associated with liver function improvement and further delisting while on treatment have been discussed above (Question 3, facts).

Pre LT recommendations

13. Patients with baseline MELD <16 (typically Child-Pugh B) have a high chance (35%) of being delisted due to clinical improvement and therefore should be treated while listed GRADE II-3
Comment: Currently, the follow up of delisted patients is very short, therefore a word of caution is to be mentioned regarding how long the clinical improvement will last and how many patients will develop an HCC

14. Patients with baseline MELD between 16 and 20 (mostly Child-Pugh C)
a. These patients have a chance of being inactivated due to clinical improvement of about 12%. They should be started on DAA while listed and the possible clinical improvement should be assessed after 12 weeks of therapy. GRADE II-3
b Patients showing a significant improvement of MELD score >3 points and albumin > 0.5g/dL after 12 weeks on DAA should be maintained on the waiting list but in inactive position and considered for possible delisting during the follow up.
c. Patients without a significant improvement in MELD and albumin after 12 weeks on DAA should be maintained in active position on the waiting list. (B1)**.** GRADE II-3

15. Patients with baseline MELD between 21 and 25 (typically advanced Child-Pugh C). A minority of these patients, specifically those with ACLF, may undergo a substantial clinical improvement after DAA treatment which makes inactivation on the waiting list still possible. For such patients a case by case multidisciplinary decision is advised**.** GRADE II-3
Comment. Since a limited MELD improvement not leading to inactivation may hamper access to LT, patients should be maintained with their baseline MELD as assessed before DAA therapy in order to counteract the MELD purgatory effect. Such a MELD exception rule should be implemented after agreement with the Organizations for Organ Procurement. <u>In addition, this candidates might benefit from receiving a graft from a suitable anti-HCV +ve donor.</u>

16. Patients with high MELD scores > 25. Based on current studies and practice, pre LT DAA treatment of these candidates is not recommended because of their poor prognosis with a significant risk of death either pre and post-LT, unknown probability of improvement, potential DAA toxicity and rapid access to LT. The option of post LT treatment with DAAs is therefore preferable. GRADE III
Comment In addition, this candidates might benefit from receiving a graft from a suitable anti-HCV +ve donor.

Q5.Patients listed for hepatocellular carcinoma (HCC): who should be treated or not before LT?

Background
Patients listed for HCC frequently have a compensated liver cirrhosis and therefore can easily tolerate DAA treatment administered to prevent HCV recurrence after LT. This aspect is particularly relevant in countries where old donors are preferentially given to HCC patients with relatively preserved liver function.

Facts

The 1-yr rate of removal from the liver transplant waiting list due to tumour progression is estimated to be up to 10% in Centres following the "Milan criteria" and up to 20% in those following "extended criteria". Similarly, the risk of dying of HCC recurrence after LT is up to 10% in centres adopting the Milan criteria and up to 20% in those adopting extended criteria. The response to therapeutic interventions for HCC while the patient is on the waiting list further affects prognosis either pre and post LT. These competing risks should be taken into account in order to avoid futile DAA treatment **(Fig.2)**

The present scenario is further complicated by the recent alert regarding a possible increased risk of HCC recurrence in patients who cleared HCV with DAAs after achieving a complete HCC eradication following resection or local ablation. As the available data are conflicting, properly designed studies are urgently needed to address this relevant issue (23-26)

Pre LT recommendations.

17. In patients listed for HCC, pre LT treatment should be restricted to those with the following features: a) a low risk of post-transplant HCC recurrence, whatever model is used to assess the risk (i.e Milan criteria, alfa-feto model or other predictive models of recurrence at listing. b) no signs of HCC progression while on HCC bridging therapy and c) a waiting time > 3 months is expected. . GRADE III . **Comment**. A decision-making algorithm is proposed in **Fig 1**

18. In patients with HCC not treated with DAA before LT, the decision and timing of DAA therapy after LT should be deferred after pathological assessment of the explanted liver. If the risk of HCC recurrence at explant pathology is high, delaying HCV treatment beyond the 2nd year post-LT is advised, unless severe form of HCV recurrence occurs. GRADE III

Comment In addition, this candidates might benefit from receiving a graft from a suitable anti-HCV +ve donor.

Q6: Is DAA therapy given across LT ("bridging therapy") a valuable option?

Background

In patients with stable clinical conditions, the full course of antiviral therapy can be generally completed before LT. Nevertheless, some patients may develop an acute complication that leads to a rapid deterioration of their liver function. Such patients may require an urgent LT and therefore this option should be specifically considered in patients who are still viremic at the time of LT or who did not achieve viral clearance for at least 30 days.

Facts

A single study from Italy (27) has recently shown that this strategy is feasible and very effective. Thirthy-one patients have been treated with SOF/RBV across transplant for up to 48 weeks and an SVR was achieved in 96% of the patients without major side effects. No data are yet available with more recent DAAs combinations.

Pre LT recommendations

19. Bridging therapy cannot be recommended on a routine basis GRADE III

20. In case of unexpected rapid deterioration of liver function while on DAA therapy, continuation of therapy across transplant can be considered particularly in patients who are still viremic. Nevertheless, the decision of continuing DAA treatment across transplant should be considered on a case-by case basis taking into account liver graft function, post operative renal function and DDI. GRADE II-3.

Q7. How to cope with failures following DAA therapy? When is detection of resistance associated substitutions (RAS) a concern?

Background. Failure to DAAs is mainly due to relapse while on-treatment virologic breakthrough is rare. Failure to multiple DAA regimens more often occurs in GT1a patients with cirrhosis, GT3 treatment experienced patients with cirrhosis, and in patients receiving shorter duration or RBV-free schedules. The majority of failures to DAA combinations are related to the presence of various proportions of HCV-RAS. A too short treatment duration or the absence of ribavirin are possible relevant cofactors. A cut off detection rate of RAS of at least 15% seems to correlate with treatment failure. NS3-4A resistance variants tend to disappear after treatment discontinuation. In contrast, NS5A RAS can affect treatment response in certain settings and these variants may persist for many years (28). The development of NS5B RAS is rare and these variants may also disappear over time.

Facts. No standardized tests for the resistance of HCV to approved drugs are available as purchasable kits. Thus far, resistance testing relies on in-house techniques with variable performances. HCV drug resistance testing is not recommended in naïve patients who are not candidate for LT as SVR is independent from the presence of NS3-4A or NS5A RAS at baseline. To date, HCV resistance testing at baseline is only recommended in the US SmPC for GZR/EBR when treating patients infected with genotype 1a. In addition resistance testing may be useful for choosing the best treatment option in cirrhotic patients infected with genotype 3 who fail multiple DAAs (29,14). If resistance testing is not available for such patients, extending treatment and adding RBV is advisable.

Pre LT recommendations

21. Assessment of RAS can be considered in situations where the presence of RAS will likely influence treatment choice and outcome. This is the case of patients with decompensated cirrhosis and infected with GT3 and of patients infected with subtype 1a under GZR/EBR as the presence of RAS justifies a longer duration of treatment or the addition of RBV. Patients with RAS that do not tolerate RBV should be treated after LT. GRADE III

22. For patients with decompensated cirrhosis who failed DAA therapy while on the waiting list, it is advisable to retreat these patients after LT. HCV resistance testing is useful for deciding retreatment GRADE III.

B. Post transplant phase.

Q8. Which DAAs should be used after LT taking into account liver function, renal function and DDI?

Background

The recipient of a liver transplant has to take life-long IS and many other drugs to treat various co-morbidities such as diabetes mellitus, hypertension, dyslipidemia etc (30). All these drugs have to be checked for possible DDI with DAA. Renal dysfunction is another common problem after LT (31) which limits the use of Sofosbuvir.

Facts

DDI with immunosuppressants.

The main DDI between DAA and IS are shown in **Table 4** and are also summarized in the EASL Recommendations on Treatment of Hepatitis C 2016 (6). SOF+DCV, SOF/LDV have no significant DDIs with any IS and antimetabolites. However potential interactions with everolimus may require additional monitoring. No data are available regarding possible interactions between SOF/VEL and major IS. Regimens containing protease inhibitors such as 2D and 3D combinations strongly interact with all major IS. SIM strongly affects the metabolism of cyclosporine A (CsA) and, to a lesser extent, of tacrolimus (Tac) and mTOR inhibitors through CYP3A4 inhibition but it has no effecton mycophenolate mofetil (MMF) metabolism. A 40%-50% increase in tacrolimus levels is to be expected during co-administration with GZR while a 15-fold increase in GZR AUC and a 2-fold increase in EBR AUC is expected if co-administered with cyclosporin (8). The combination of SOF/LDV has minor interactions with CsA, Tac and mTOR inhibitors (6). In addition to the forementioned DDI, DAAs-related HCV clearance can accelerate the metabolism of various IS (11) by improving the metabolic functions of the liver.

Possible DDI between DAA and other frequently prescribed drugs (6, 32) should be taken into account particularly when antifungal agents, cardiovascular drugs, statins and CNS drugs are administered simultaneously.

Renal function impairment

Renal dysfunction is frequent after LT either due to early postoperative complications such as acute tubular necrosis or as a result of long-term exposure to CNI. HCV-related kidney injury, diabetes and hypertension are other possible factors impairing kidney function. This is why the majority of LT recipients present a 30% GFR decline after one year from LT and a 15%–20% prevalence of severe renal impairment (estimated GFR<30 mL/min) after 5 years (33).

Recommendations post LT

23. SOF+DCV, SOF/VEL can be given safely in combination with any immunosuppressant (IS). Since SOF/LDV moderately affects CNI/mTOR metabolism, the blood levels of IS should be monitored. SIM, GZR and EBR should not be co-administered with CsA. Monitoring blood levels is required when SIM, GZR and EBR are combined with Tac or mTOR inhibitors. 2D and 3D combinations require monitoring of all major IS. Therefore, SOF+DCV or SOF/LDV should be the preferred regimens after LT due to no or minimal DDI; (GRADE II-2).

24. Any other drug co-administered with DAAs after LT should be checked for possible DDI, such as antifungal agents, antibiotics, cardiovascular drugs, CNS drugs, recreational drugs and even hormonal treatments. Given the frequent occurrence of arrhythmia after LT, close attention should be paid to patients treated with DAAs. Amiodarone should be avoided as per recent recommendations (6) GRADE II-2.

25. SOF requires dose adjustment when the estimated GFR is below 30 mL/min. Although no firm recommendation can be made on the extent of the dose adjustment (6), SOF administration every other day is currently used with an acceptable risk/benefit ratio. Although tolerability and efficacy of GZR/EBR are satisfactory in patients with renal insufficiency, their use is not recommended after LT due to major DDI with many IS. This is also true for the 3D combo. GRADE II-3.

26. The issue of an increased risk of rejection following HCV clearance is of concern but needs to be evaluated in properly designed studies. In the meantime close monitoring of CNI/mTOR is recommended particularly at the end of DAA therapy when the cessation of DDIs and the improved metabolic capacity of the liver may alter the exposure to various IS. (11). GRADE III

Q9. What rate of sustained virological response is expected after treating patients for HCV disease recurrence?

Background

The natural course of hepatitis C is significantly accelerated in LT recipients when compared to immunocompetent individuals with 15% to 30% of the patients progressing to cirrhosis within 5 years from LT and approximately 50% developing liver failure shortly thereafter. A subset of patients (2%-9%) may develop FCH which is defined by progressive cholestasis, very high HCV-RNA levels, hepatocyte ballooning and rapid progression to graft failure (1-3). The management of HCV recurrence has been a challenge in the era of IFN-based therapies due to the combined effect of limited efficacy, risk of rejection (34) and high toxicity of IFN. This sequence of events explains why HCV positive recipients had a 10%-reduced graft and patient survival when compared to other indications for LT. However, IFN-induced SVR significantly improved outcomes after LT, resulting in 5-year survival rates similar to those for HCV-negative patients (35). As the new DAAs are much more effective and far better tolerated than IFN-based regimes, the outcome of LT for HCV recipients is expected to improve and become similar to that of patients with non HCV indications.

Facts

Considering patients with HCV recurrence after LT, the virological response to DAA has been

assessed in 14 studies (11-12, 14, 36–46) dealing mainly with experienced GT1 patients. Results from the main studies are summarized in **table 5** and **6** which separate patients according to severity of liver disease, type of DAA regimen and HCV genotypes.

Mild fibrosis stages and compensated cirrhosis (Child-Pugh A) (table 5). SVR was achieved in more than 90% of patients, with a good safety profile. In SOLAR 1 study (11), the combination of SOF/LDV+RBV (1000-1200 mg) given to patients with genotype 1 or 4 infection, resulted in SVR-12 rates higher than 90% irrespective of treatment duration (12 or 24 weeks). Similar excellent SVRs of about 90% have been reported with SOF+SIM (39) in patients infected with Genotype 1, 2 or 4 but not in those infected with genotype 3 where the SVR was only 60%. The 3D combination (37) was equally effective only when administered to patients without cirrhosis. Finally SOF+DCV was very effective in all patients but those with decompensated cirrhosis (14). In patients not eligible for RBV, the optimal duration of treatment is unknown but SOF/LDV for 24 weeks in GT 1 and 4 patients seems to be a reasonable option post LT (8). Although RBV has been associated in most DAA regimens after LT, its use may be problematic due to renal impairment. Indeed, in a recent study focusing on treatment of HCV infection after kidney transplantation, SOF/LDV for 12 or 24 weeks in G1/4 without RBV resulted in SVR rates of 96 to 100% indicating that excellent results can also be achieved in immunodepressed patients without RBV (47)

De-compensated cirrhosis.
When considering patients with decompensated cirrhosis after LT, the SVR rates were 10% to 30% lower than what is generally observed in patients without decompensation (11-12, 43) **(table 6).** Interestingly, although SVR rate around 85% in Child Pugh B has been reported in the SOLAR 1 study (11), this result was not confirmed in the SOLAR 2 study where post-LT SVR was 95% and 100% in patients treated for 12 and 24 weeks respectively (12). An improvement in MELD and CP scores has been reported in 50%-60% of patients after treatment with different DAA combinations such as SOF+DCV, DCV +SIM (46) or SOF/LDV + RBV (600 mg increased as tolerated) (11,12). On average, the improvement was of 2 points for CP score and 3 points for MELD score.

Fibrosing cholestatic hepatitis (FCH)
In the French multicentre cohort CUPILT (45), SVR 12 rates of 88% and 100% were obtained in patients with strictly defined severe forms of FCH treated with SOF+RBV or SOF+DCV±RBV (600 mg increased as tolerated) for 24 weeks. There was no graft loss at the end of follow-up and a significant improvement in liver graft function was constantly observed. Studies based on smaller numbers of patients with FCH confirmed these excellent results in patients with FCH treated with SOF/LDV+RBV for 12 or 24 weeks (11, 12) (table 2 post LT). An improvement in MELD and CP scores has also been reported in patients with FCH after treatment with SOF + DCV or DCV+ SIM (41).

SVR according to genotypes
- Genotype 1a: when SOF+SIM is given to patients with advanced fibrosis (F3-F4) the expected SVR rate is about 80% (**table 5)** which is at least 10% lower than that observed in patients infected with genotype 1b with or without advanced fibrosis. (39, 41-42).
– Genotype 3: For patients without cirrhosis the combination SOF+DCV±RBV (1000-1200 mg/die) resulted in excellent results with SVR of about 90% (15). For patients with cirrhosis the optimal DAA combination and duration are still to be defined. The promising SVR rate of 85% obtained with SOF/VEL+ RBV (14) given to immunocompetent subjects with decompensated cirrhosis needs to be verified in the transplant setting.

Recommendations

27. Early treatment of FCH with SOF+DCV+RBV RBV(600 mg, increased as tolerated) for 24 weeks or SOF/LDV +RBV RBV (600 mg, increased as tolerated) for 12 weeks is recommended GRADE II-1. SOF + VEL might be an alternative option, but no published data are available to date. (GRADE III)

28. LT recipients with Genotype1/4, infection can be treated in the same way as non-transplant patients in terms of combinations of DAA and duration of treatment. In particular, SOF/LDV ± RBV or SOF+DCV for 12 weeks are recommended. The same combinations should be used for 24 weeks in patients not eligible to RBV. If the 3D combo is considered, careful monitoring of CNI trough levels is advised as strong DDI are expected. GRADE II-1.

29. LT recipients with GT1a advanced fibrosis (F3-F4) should not be treated with SOF+SIM because of lower SVR rates (- 10%) compared to other DAA combinations. GRADE II-2

30. LT recipients with Genotype 3 infection without cirrhosis or with compensated cirrhosis, should be treated with SOF +DCV+RBV for 12 weeks or with SOF + DCV without RBV for 24 weeks in case of ineligibility to RBV (GRADE II-1). The combination of SOF/VEL±RBV for 12 weeks should be tested urgently in the LT setting GRADE III. IFN is not recommended post-LT to limit the risk of IFN-induced rejection. GRADE III

31. Renal function impairment and frequent use of drugs at risk of DDI (www.hepcdruginteractions.com) may limit the use of some DAAs in the post LT phase. DAA regimens should therefore be used for LT patients, as described in Recommendations 23 to 25 GRADE II-2

Q10. What is the best timing for DAA treatment after LT?

Background

In patients with active HCV replication before LT, post-transplant HCV recurrence is rapid and virtually universal. HCV RNA can be detected as early as a few hours post-transplant (48) and HCV graft reinfection subsequently leads to symptomatic HCV hepatitis between 1 to 4 months post-LT, with variable clinical patterns. Two different approaches can be considered to overcome the deleterious consequences of HCV recurrence post -LT:

1. Very early or early DAA treatment, before biochemical manifestations of HCV recurrence develop i.e. pre-emptive therapy
2. Later treatment initiated in response to biochemical and histopathological evidence of HCV recurrence, i.e. clinically oriented treatment.

In the IFN/RBV era, pre-emptive therapy was found to be ineffective and difficult to manage (49), due to severe hematological side effects and risk of rejection in the early post-LT period. Pre-emptive treatment has therefore never been adopted as the standard of care.

3. Treatment of patients with histologically-proven HCV recurrence and minimal fibrosis (stage F1-F2 in the METAVIR scoring system was the norm) (50, 51). Given the far better risk-benefit ratio of DAA therapy, those principles of management can be reconsidered.

Facts
Results from Phase 3 studies show that excellent SVR rates > 93% can be achieved with DAA therapy in patients with HCV-related chronic active hepatitis and Child Pugh A cirrhosis or FCH post-transplant. SVR rates are lower in patients with decompensated cirrhosis (see above). Although very early DAA-based pre-emptive therapy may be an attractive option to manage HCV recurrence, no large data are currently available on the efficacy and safety of this approach. Of note, in the very early post-transplant phase optimal use of DAA may be hampered by reduced postoperative liver function, impaired renal function and DDI.

Post LT recommendations

32. At present, pre-emptive DAA therapy cannot be recommended on a routine basis. Prospective studies generating data on the efficacy, safety, optimal dose, timing and duration of pre-emptive treatment should be encouraged to assess the benefit of DAA regimens in this setting. GRADE III

33. DAA treatment of HCV recurrence should be considered in any LT recipient as early as clinically feasible, irrespective of fibrosis stage. The aim is to prevent progression to cirrhosis and to maximize SVR. Initiation of DAA therapy between 3 and 6 month post LT is encouraged. GRADE III.

Q11. Can we expect a beneficial effect of HCV therapy on extra-hepatic manifestations of HCV, irrespective of liver injury?

Background
Active HCV replication after LT is involved in a number of extra-hepatic manifestations. HCV is a well-established independent risk factor for post-LT renal function impairment (33), insulin resistance and diabetes mellitus (52). HCV is also a major etiological factor for type 2 cryoglobulinemia post-LT (53) and a co-factor facilitating poly- or monoclonal B-cell proliferation (54-55). Diabetes mellitus and renal impairment are independent negative predictors of survival post-LT (33, 56). Improved renal function after achieving SVR post-LT was observed in the IFN/RBV era (57). In immunocompetent subjects, SVR has also been shown to reduce the risk of renal impairment and cardiovascular-related morbidity (58).

Facts
The impact of DAA on renal function and glucose metabolism post-LT has not yet been evaluated in Phase 3 prospective clinical trials or in retrospective investigator-driven studies, which so far have focused on SVR, liver function and safety as the primary and secondary endpoints.

Recommendations

34. A beneficial effect of DAA on extra-hepatic manifestations of HCV post-LT is an attractive hypothesis that may contribute to improved long-term outcomes. The impact of DAA treatment on renal function and insulin resistance post-LT should be considered as secondary endpoints in forthcoming prospective clinical trials or observational studies. GRADE III

35. DAA treatment should be considered on an individual basis in the event of post-LT renal dysfunction or insulin resistance, irrespective of liver disease. GRADE III

36. In the case of post-LT symptomatic mixed cryoglobulinemia or HCV-associated malignant B-cell proliferation, DAA treatment should be used as in the non- transplant setting (6). GRADE III

Q12. Is re-transplantation for HCV-infected recipients a reliable option under DAA therapy?

Background

The utility of re-transplantation for severe HCV recurrence with decompensated cirrhosis has been controversial due to poor results in patients with pronounced hyperbilirubinemia (> 5 mg/dL), renal dysfunction or MELD score > 28 (59-60). The significant burden of re-transplantation is also a consideration in LT programmes with a high prevalence of HCV-related primary liver transplants, such as in southern European countries or in the USA.

Facts

It is unknown how DAA therapies may impact the outcome of re-transplantation for severe HCV recurrence. The issue has not been addressed in any published clinical trials. Treatment of severe recurrence after primary LT has been reported to improve liver function (43-46) and may therefore reduce the need for re-transplantation. DAA therapies are likely to improve outcome because viral clearance can be achieved either before or after re-transplantation.

Recommendations

37. Outcome of re-transplantation due to HCV-related primary graft loss should be re-assessed in the DAA era by prospective, observational studies which specifically target this population. GRADE III.

38. Re-transplantation can be considered on a case-by-case basis, taking into account the intrinsic risks of re-transplantation and organ availability GRADE III.

Q13. Can HCV-positive donors be used more extensively?

Background

Depending on the geographical area, the prevalence of HCV among organ donors ranges from 1.4% to 5.5% (61-63) and is 2 to 3-fold higher than in the general population. Due to variations in HCV replication in highly selected donors, transmission of HCV is not universal. It occurs in roughly 50% of recipients of a graft from a HCV-positive donor. The use of HCV-positive liver or kidney grafts in HCV-positive recipients has been encouraged by health authorities on the grounds that a 5-year liver (63-65) or kidney graft function is similar to that observed with organs from HCV-negative donors. Yet HCV-positive organs remained under-used (66) because of reluctance on the part of health care professionals. Caution was heightened in the IFN era because of poorer outcomes associated with HCV-positive donors older than 50 years (67). The possibility of recipients acquiring the donor HCV genotype was also of concern in the case of G1/ G3 donor-recipient mismatching. The high pangenotypic efficacy of DAA regimens may render HCV-positive liver grafts safer and may extend use of such grafts even in HCV-negative recipients, enabling a substantial expansion of the donor pool. This debate has been recently opened in the kidney transplant community. The chair of the Ethics Committee of UNOS and the co-chair of the American Society of Transplant Surgeons have both recently argued in favor of the use of HCV-positive kidneys in HCV- negative recipients (68).

Facts

To date, DAAs have not been tested after LT in patients receiving a graft from an HCV-positive donor. The risk/benefit ratio of engrafting HCV-positive organs deserves re-assessment in both HCV-positive and HCV-negative recipients. This may be particularly important in G1 recipients receiving G3 liver grafts, because of inferior SVR rates observed in G3 before the VEL becomes available. Using such grafts in candidates with previous SVR to anti-HCV therapy is also illogical and unethical although the risk/benefit ratio of such a policy may again merit assessment in urgent situations.

Recommendations

39. Given the current under-use of HCV+ve organs**,** clinical studies under the control of ethical authorities should be designed for both HCV-positive and HCV-negative recipients. The aim would be to evaluate the impact of an anti-HCV positive donor on virological outcome, graft and patient survival. The impact on the donor pool should also be studied (GRADE III).

40. In general, liver grafts from HCV-positive donors should not be transplanted to HCV-positive candidates in whom HCV has been previously eradicated before LT, for both ethical and cost-effectiveness reasons (GRADE III). However in case of rare urgent situations, when the risk of death outweighs the risk of using an HCV+ve graft in a previously treated patient, a HCV positive organ may be considered again after obtaining candidate's or relatives' informed consent (GRADE III).

41. In candidates with decompensated cirrhosis and medium MELD scores and in candidates with HCC in whom a long waiting time can be expected, treatment of HCV infection before LT should be balanced against the benefit of accelerated access to LT through the use of a HCV positive liver graft. (GRADE III).

Conclusions:

Data accumulated over the last 3 years on the use of DAAs pre and post-LT opened the door to considerable changes in the treatment of Hep C in the liver transplantation field. ELITA therefore decided to compile this series of "Consensus statements" which focus primarily on very specific LT issues that had not been extensively addressed previously. They have been developed in order to be of support to physicians and other stakeholders in charge of LT candidates and recipients when deciding to treat Hep C especially in some difficult situations. These "Consensus statements" are a starting point and will be up-dated on a regular basis, because of the rapid changes in knowledge and rapid availability of new compounds. We are aware that some questions are still waiting for an answer. For example: Will delisting due to clinical improvement be a safe and sustainable option? What may be the risk of HCC in patients delisted after DAA treatment? What is the impact of DAA on extra-hepatic manifestations of HCV? What will the impact of DAAs on re-transplantation be? Will DAAs allow a wider use of HCV positive grafts? How these guidelines apply to programs with a high proportion of LDLT?

ELITA is open to support multinational European initiatives to specifically address all these open questions.

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Legenda Fig 1
Patients listed for de-compensated cirrhosis or HCC: factors to be taken into account in the decision making process before DAA treatment

SUPPLEMENTARY MATERIA

Journal of Hepatology
CTAT methods

Tables for a "Complete, Transparent, Accurate and Timely account" (CTAT) are now mandatory for all revised submissions. The aim is to enhance the reproducibility of methods.

- Only include the parts relevant to your study
- Refer to the CTAT in the main text as 'Supplementary CTAT Table'
- Do not add subheadings
- Add as many rows as needed to include all information
- Only include one item per row

If the CTAT form is not relevant to your study, please outline the reasons why:

We are submitting a consensus statement; the CTAT does not apply.

1.1 Antibodies

Name	Citation	Supplier	Cat no.	Clone no.

1.2 Cell lines

Name	Citation	Supplier	Cat no.	Passage no.	Authentication test method

1.3 Organisms

Name	Citation	Supplier	Strain	Sex	Age	Overall n number

1.4 Sequence based reagents

Name	Sequence	Supplier

1.5 Biological samples

Description	Source	Identifier

1.6 Deposited data

Name of repository	Identifier	Link

1.7 Software

Software name	Manufacturer	Version

1.8 Other (e.g., drugs, proteins, vectors etc.)

1.9 Please provide the details of the corresponding methods author for the manuscript:

Journal of Hepatology

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b)	Identify the source and authentication of cell lines	
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b. Include the study protocol and statistical plan

e) Identify the inclusion/exclusion criteria in the selection process for the patients included in the study

4) Statistics

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a) When using public databases:

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a. Protein, DNA and RNA sequences

b. Microarray data

Deposition is strongly recommended for many other datasets for which structured public repositories exist

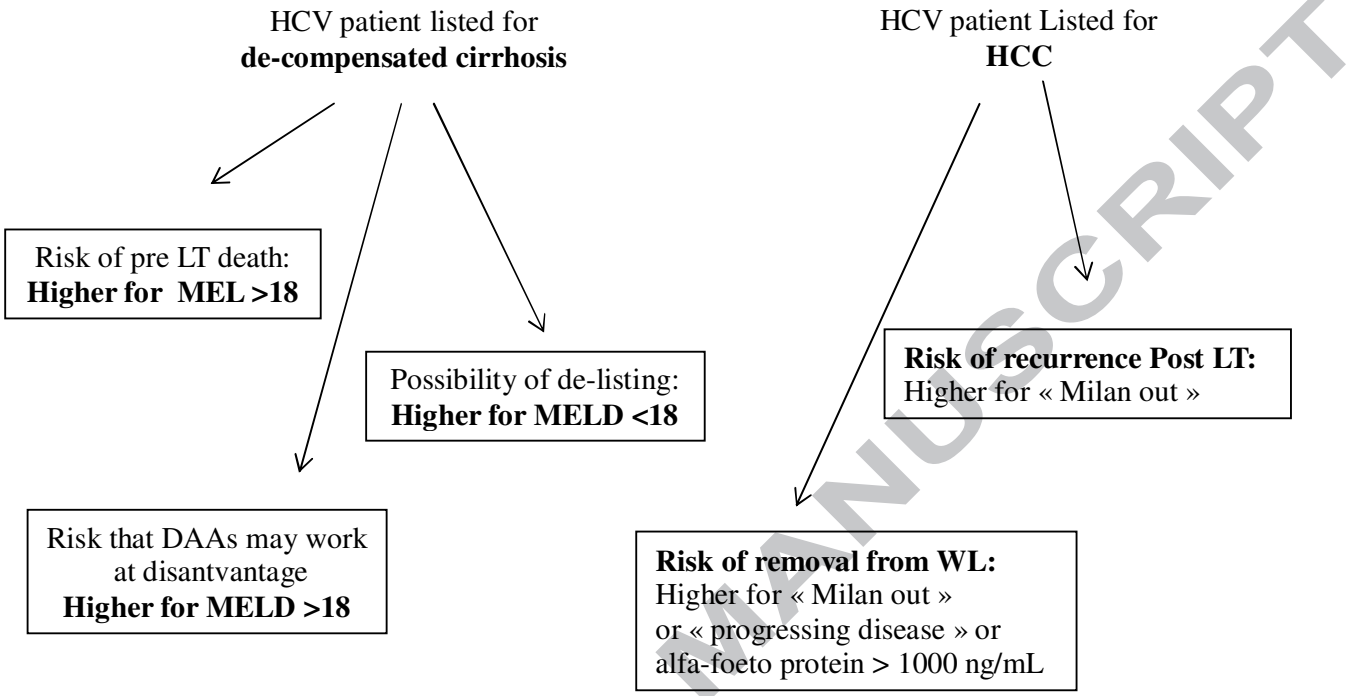

Table 1 GRADE system used in the EASL Clinica Practice Guidelines.

Grade evidence	
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, uncontrolled experiments
III	Opinions of respected authorities

Table 2a and 2b Exposure of DAA in case of impairment of liver (table 2a) or kidney function (table 2b)

Table 2a

	Liver Impairment (AUC fold-effect)			Dosing guidelines (EMEA)
	Mild*	***Moderate****	***Severe****	
Simeprevir		⇑2.44	⇑5.22	OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B or C)
Sofosbuvir GS331007		⇑2.26 (1.18**)	2.43 (1.09**)	No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C).
Ledipasvir	no adjustment	no adjustment	↔	**No dose adjustment.** Treatment with Harvoni should be guided by an assessment of the potential benefits and risks for the individual patient
Paritaprevir/r	⇓0.52	⇑1.62	⇑10.23	Viekirax +/- Exviera is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C)
Ombitasvir	0.92	0.70	0.45	
Dasabuvir	1.17	0.84	4.19	
Daclatasvir	⇓0.57	⇓ 0.62 unbound	⇓0.64 unbound	No dose adjustment for CPT Class A or B. Lower SVR rates were observed with CPT C compared with CPT A or B in ALLY-1, thus treatment for 24 weeks is recommended (EASL guidelines)
Velpatasvir		↔	↔	No dose adjustment of Epclusa is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C). Safety and efficacy of Epclusa have been assessed in patients with CPT Class B cirrhosis, but not in patients with CPT Class C cirrhosis
Grazoprevir	⇑1.66	⇑4.82	⇑11.68	No dose adjustment of ZEPATIER is required in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C)
Elbasvir	⇓0.61	⇓0.72	⇓0.88	

* Typically Mid = CPT A, Moderate = CPT B, Severe = CPT C

** Cmax reduced ↔

Renal Impairment (AUC fold-effect)

	Mild *eGFR 60-90****	***Moderate*** *eGFR 30-60**	***Severe*** *eGFR < 30*	***Haemodialysis***
Simeprevir			↑1.62	*ND*[†]
Sofosbuvir *(GS331007)*	↑1.61* *(↑1.55)**	↑2.07* *(↑1.88)**	↑2.71* *(↑5.51)**	↑1.28, 1.60** *(↑13.8, 21.7)***
Ledipasvir			↔	*ND*[†]
Paritaprevir/r	↑1.19	↑1.33	↑1.45	*ND*
Ombitasvir	↔	↔	↔	*ND*
Dasabuvir	↑1.21	↑1.37	↑1.50	*ND*
Daclatasvir	↑1.18[∇]	↑1.39[∇]	↑1.51[∇]	↑1.27[∇]
Velpatasvir			↑1.50	ND
Gazoprevir			↑1.65	↔
Elbasvir			↑1.86	↔

* eGFR: Mild typically in the range 50 or 60 mil/min to 80 or 90. Moderate: typically in the range 30 to 50 or 60 ml/min Severe <30 ml/min

Table 3. DAAs in patients with decompensated cirrhosis

	Afdhal Ref.10	Charlton Ref.11	Manns Ref.12	Foster Ref.13	Poordad Ref.15	Curry Ref 14
Pts, N	50	108	160	467	60	267
Therapy	SOF+ R	SOF/LDV+r R	SOF/LDV+ R	SOF/LDV+R SOF+DVC+R	SOF+DCV+R	SOF/VPV±R
Duration Tx	48w	12w (53 pts) 24w (55 pts)	12w (78pts) 24w (82pts)	12w	12w	12 w (180 pts) 24 w (87pts)
Child A, N of pts	18	0	0	112	12	16
Child B, N of pts	32	59	78	309	32	240
Child C, N of pts		49	82	46	16	11
MELD	>15: 4 pts		>15: 41 pts	Mean (range) 11.9 (6-36)	>15: 14 pts	>15:13 pts
Tx-experinced %	80%		78%	47.1%	60%	80%
GT1a-1b, % GT2-3-4, %	38%-30% 32%		47.5%-42.5% GT4: 10%	GT1 50.3% Other: 49.7%	57%-18% 8%-17%	78% 22%
SVR12 % Child A% Child B-C%	78% 68%	88%	85-88%	SOF/LDV: 80% SOF+DCV:74 %	92% 94%-56%	SOF/VPV 83% SOF/VPV+RBV: 94%

Table 4 Drug-drug interactions between HCV DAAs and immunosuppressants

	SOF	SOF/ LDV	SOF/ VPV	3D	GZR/ EBR	DCV	SIM
Aza							
CsA							
Etanercept							
Everolimus							
Mycofenolate							
Sirolimus							
Tacrolimus							

Color legend

No clinically significant interaction expected

Potential interaction that may require a dosage adjustment

These drugs should not be co-administered

Table 5: DAA for HCV recurrence after liver transplantation in mild fibrosis and compensated cirrhosis

	Charlton (38)	Gutteriez (39)	Faisal (40)	Brown (41)	Pungpagong (42)	Kwo CORAL-1 (37)	Poordad Ally-1 (15)	Charlton Solar 1 (11)	Manns Solar 2 (12)
Pts (n)	40	61	120	151	123	34	53	162	168
Therapy	SOF+RBV 24 w	SOF/SIM ±RBV 12w	SOF+SIM ±RBV 12w Or SOF/RBV 24w or SOF/LED 12 to 24w	SOF+SIM ±RBV (21%, starting dose 800 mg) 12w	SOF+SIM/ ±RBV 12w	3D combo ** +RBV 24w	SOF+DCV+ RBV 12w	SOF/LED +RBV 12 vs 24 w	SOF/LED +RBV 12 vs 24 w
Genotype 1-4/2-3	83% (1a55%-1b28%)-3%/15%	All GT1 1a:57% 1b: 43%	GT1 83%	All pts GT1* GT1a 56.3%	All GT 1* GT1a 60% G1b 35%	GT1a 85% GT1b	GT1: 77% 1a: 58% 1b: 19% GT3: 21%	GT1 99% G1a 70% G1b 29%	GT1: 87% 1a: 49% 1b: 38% GT4: 13%

				G1b 26.9%			GT6: 2%		
Treatment-experienced	88%	69%	82%	56.3%	82%	71%	58%	82%	81.5%
F3/F4	62%	38%	48%	64.2% (F4)	30%	0	55%	29.6% (F4)	40% (F4)
SVR 12 Overall	70%	93.4%	85%	88%	90%	97%	94%	97% Similar between 12 vs 24w	97%
GT 1	GT1a: 73% GT1b 55%	GT1a: 89% GT1b 100%	GT1a 83% GT1B 100%	GT1a 85% GT1b: 94%	GT1a: 86% GT1b 95% (ns)	GT1a: 97% GT1b 100 % (ns)	GT1 95% GT1a: 97% GT1b 90 % (ns)	NA	GT1: 97%
GT3/4	100%/-	NA	100%	NA		NA	91%/-	NA	-/95%
F0-F2/F3-F4	NA		91%/81%	93%/86%	93% vs 81% p=0.05	NA	NA	Similar SVR	97%/97%¥
GT1aF3-4	NA	67%		82%	71% (vs 93%)	NA	NA	NA	NA
Relapse/ Breakthrough	30%/-	Higher Among GT1a F3/4	6%/0.8%	7%/0.6%	6.5%/2.4%	3%/-	NA	1.2%/0	
SAE	5% Anemia 20%	low	Severe anemia 13%	11.9%	1.6%	6%	0%	15%	

DCV : daclatasvir, GT : genotype, LED: ledispavir, NA : not applicable, ns : not significant, Pts : patients, RBV : ribavirin, SAE : serious adverse event, SOF : sofosbuvir, SIM : simeprevir.

Table 6: DAA for severe HCV recurrence after liver transplantation de- compensated cirrhosis and fibrosing cholestatic hepatitis

	Fibrosing Cholestatic Hepatitis			De-compensated cirrhosis		
	Forns§ (43)	Charlton + Manns Solar 1 + 2 (11, 12)	Leroy (CUPILT) (45)	Fontana* (46)	Charlton Solar 1 (11)	Manns Solar 2 (12)
Pts (n)	52	11	22	97	61	53
Therapy	SOF+RBV or SOF+RBV+PEG 24w	SOF+ LEDI +RBV 12 vs 24 w	SOF+RBV+ /- PEG or SOF/DAC 24w	DCV+SOF+/- RBV(n=77); DCV/SIM+/- RBV (n=18) 24w	SOF/LED+RBV 12 vs 24 w	SOF/LED + RBV 12 vs 24 w
Genotype 1-4/2-3	GT1: 86% GT1a : 42% GT1b : 44% GT2/3: 4% GT4: 10%	All GT1 GT1a : 82% GT1b : 18%		GT 1: 93% GT1a: 39% G1b: 47% GT3 : 2% GT4: 4%	GT1 98.6% G1a 74% G1b 24.6% G4: 1.4%	GT1: 85.6% 1a: 49% 1b: 39.6% GT4: 11.4%
Treatment-experienced	NA	82%		55% before LT 37% after LT	85%	83%
Child Pugh B/C	NA	NA	NA	31%/12% Cholestatic pattern : 37%	85%/15%	85%/15%
SVR 12 Overall	73%	100% Similar SVR in w12 & w24	88% vs 100% SOF/RBV vs SOF+DCV+ RBV	87% DCV+SOF vs DCV+SIM 91% vs 72% (p=0.047) RBV+ vs RBV- : ns	83.6% 12 vs 24w 80% vs 86.6%	92.4% 12 vs 24w 88% vs 93.1%
GT 1	NA	GT1a: 100% GT1b: 100%		NA	NA	GT1: 93.6%
GT3/4	NA	NA			NA	-/83.3%**
Child Pugh B/C	NA	NA	NA	NA Cholestatic vs non cholestatic 86%vs 87% p>0.99	86.5% vs 66.6%*	97.7% vs 62.5% ¥
GT1aF3-4	NA	NA	NA	NA	NA	NA
Relapse/ Breakthrough	8%/-	0/0		2%/5% (All with DCV+SIM)	6.5%/0	1.8%/-
SAE	2 % drug discontinuation due to SAE Death 13%	27% No study drug discontinuation		20% 2 SAE possibly related to DAA No drug interruption	No SAE leading to study drug discontinuation	26%
Improvement of liver function	Decrease in bilirubin from 4.7 to 0.7mg/dL Median of 8 MELD points improvement	Normalization of INR , bilirubin and Albumin on posttreatment week 4	100% Normalization of LFT in the CUPILT study	*Average CP /MELD improvement :* 1 /2.3pts *% of CP/MELD deterioration :* 13%/17%	*% of CP/MELD improvement:* 59%/45% *Average CP/MELD improvement* :2.2 /3.3pt *% of CP/MELD deterioration*: 7%/18% (only in CP B) Decrease in bilirubin by 0.5 & 1.5 mg/dL, in CPB and CPC , respectively, increase in albumin by 0.5 g/dL	*% of CP/MELD improvement* 77%/60% *Average CP/MELD improvement :* 1.8/3.5pt *% of CP/MELD deterioration:* 2.5%/23%

§ Early severe recurrent hepatitis; * 43% CP B/C, 37% cholestatic pattern on cirrhosis; * Only 9 Child Pugh C patients;
** only 6 GT4 pts; ¥ only 8 Child Pugh C pts.

CP : Child-Pugh, DCV : daclatasvir, GT : genotype, LED: ledispavir , NA : not applicable, ns : not significant, pt: points, PEG : pegylated Interferon, Pts : patients, RBV : ribavirin, SAE : serious adverse event, SOF : sofosbuvir, SIM : simeprevir, SVR : sustained virological response.